REMARKS

This submission is in response to the final Official Action dated March 5, 2003. Claim 25 has been amended. Applicants understand that claims 37 and 38 will be examined upon the allowance of a generic claim. Non-elected claims 39-49 have been cancelled, without prejudice or disclaimer. New claims 50-55 have been added. Accordingly, claims 25-33, 35-38, and 50-55 are pending and at issue. Reconsideration of the above identified application, in view of the amended claims and the following remarks, is respectfully requested.

Claim 25 has been amended to recite that the antimicrobial coating is immobilized on a surface of the article, and that the antimicrobial metallic material is bound to the nitrogen-containing polycationic polymer matrix. Support for this amendment can be found throughout the application, as well as in the priority application PCT/US94/14636, filed December 19, 1994, a copy of which was attached to Applicants previous response, filed December 5, 2002, as Exhibit B. Selected sections of support for this claim is can be found in the Claim Support chart below.

New claims 50-55 are fully supported by the disclosure, as well as by the above-cited priority application, as set forth in the Claim Support chart below.

Claim Support Chart (emphasis added)

Claim	Exemplary Cite - Instant Sp c.	Ex mplary Cite - PCT/US94/14636
25	*Page 17, 3rd paragraph*: A preferred class of materials are those having the aforementioned properties, which are capable of being immobilized on a surface and which preferentially bind a bactericidal metallic material in such a manner so as to permit release of the metallic biocide to the microorganism but not to the contacting environment. Most preferred is the class of organic materials which can dissolve into, adhere to, disrupt or penetrate the lipid bilayer membrane of a microorganism. For this purpose, surface active agents, such as cationic compounds, polycationic compounds, anionic compounds, polyanionic compounds, non-ionic compounds, polyanionic compounds or zwitterionic compounds may be used. *Page 21, 1st full paragraph*: In this embodiment, the silver salt is attached to or impregnated into the matrix and on the tentacles of the polymer such that the silver is substantially non-leachable. Again, not wishing to be bound by theory, it is believed that the silver salt forms complexes with functional groups in the polymer, and that the complexed silver resists leaching into ambient liquids or other materials (e.g., creams or gels) in contact with the coated surface.	*Page 15, 2nd paragraph*: Non-metallic antimicrobial agents useful for this purpose include any anti-bacterial, anti-viral and/or anti-fungal materials which are capable of being immobilized on a surface and which are compatible with the sterile liquid. Most preferred are the class of agents which cause dissolution of the lipid bilayer membrane of a microorganism. For this purpose, surface active agents, compounds such as cationic or polycationic compounds, anionic or polyanionic compounds, non-ionic compounds and zwitterionic compounds may be used. *Page 22, 2nd full paragraph*: In a preferred embodiment, glass beads coated with metallic silver or a silver salt are added to the sterile liquid. The silver compound is attached to the beads such that the silver is substantially non-leachable.
50, 51, 52, 53, 54, 55	*Page 17-18, bridging paragraph*: Organic materials which currently are most preferred for use in the invention include cationic or polycationic compounds such as biguanide compounds. These may be attached to and immobilized on a substrate, or used to form the matrix of a freestanding film, by any appropriate method, including covalent bonding, ionic interaction, coulombic interaction, hydrogen bonding, crosslinking (e.g., as crosslinked (cured) networks) or as interpenetrating networks, for example. *Page 18, last paragraph*: Preferred	*Page 15, 2nd paragraph*: Preferred agents include biguanide compounds or benzalkonium compounds. These agents may be attached to the substrate by covalent bonding, ionic interaction, coulombic interaction, hydrogen bonding, crosslinking (e.g., as crosslinked (cured) networks) or as interpenetrating networks, for example. *Page 19-20, bridging paragraph*: Preferred compounds include, e.g., chlorhexidine or polyhexamethylene biguanide (both available from Zeneca of Wilmington, Del.).

	compounds include, e.g., chlorhexidine (available from Aldrich Chemical Co., Milwaukee, Wis.) or polyhexamethylene biguanide (available from Zeneca Biocides, Inc. of Wilmington, Del.). The above-mentioned organic materials may be modified to include a thiol group in their structure so as to allow for the bonding of the compound to a metallic substrate, or may be derivatized with other functional groups to permit direct immobilization on a non-metallic substrate. For example, the above-mentioned organic materials may be suitably functionalized to incorporate groups such as hydroxy, amine, halogen, epoxy, alkyl or alkoxy silyl functionalities to enable direct immobilization to a surface.	These compounds may be modified to include a thiol group in their structure so as to allow for the bonding of the compound to the metallic surface of the filter. Alternatively, these compounds may be derivatized with other functional groups to permit direct immobilization on a non-metallic surface. For example, the above-mentioned antimicrobials may be suitably functionalized to incorporate groups such as hydroxy, amine, halogen, epoxy, alkyl or alkoxy silyl functionalities to enable direct immobilization to the surface in lieu of a metal.

These sections describe important features of the claims as amended herewith, *i.e.*, that the antimicrobial metallic material is non-leachably bound to, *e.g.*, dispersed or impregnated in, the matrix, and that the polymer matrix is immobilized on the surface of the article.

No new matter has been added by way of this amendment. Each of the Examiner's rejections is discussed below.

Anticipation

The Examiner has rejected all claims as allegedly as being anticipated under 35 U.S.C. §102(b) by Mermel et al., 1993 (the "**Mermel Publication**"), contending that the Mermel Publication discloses a catheter coating which exhibits antimicrobial surface activity.

It is respectfully submitted that the Mermel Publication fails to anticipate the claimed invention as set forth by the amended claims. Briefly, the Mermel Publication compares various types of coated catheters, only one of which comprises a metal; the chlorhexidine-silver-sulfadiazine-impregnated catheter (see, Mermel Publication, page 920, 2nd column, 2nd full paragraph). As discussed below, this catheter was specifically shown by the Mermel Publication to leach biocidal amounts into it's surrounding environment.

As in the previous amendment, filed December 5, 2002, the Examiner's attention is respectfully directed to Table 1 on page 922 of the Mermel Publication. This table describes the results of testing antimicrobial activity of the catheters when embedded vertically into agar that contained bacteria. In the last row of Table 1, it is shown that the chlorhexidine-silver-sulfadiazine catheter resulted in a mean zone of inhibition, *i.e.*, antimicrobial activity at a distance from the catheter, of between 3-11 mm. This could not have taken place by any other mechanism than by leaching of biocidal amounts of one or more components into the surrounding agar, thus killing bacteria at a distance from the catheter. To further clarify the "leaching" from the catheters, the design of the experiments described in the Mermel Publication are schematically depicted below.

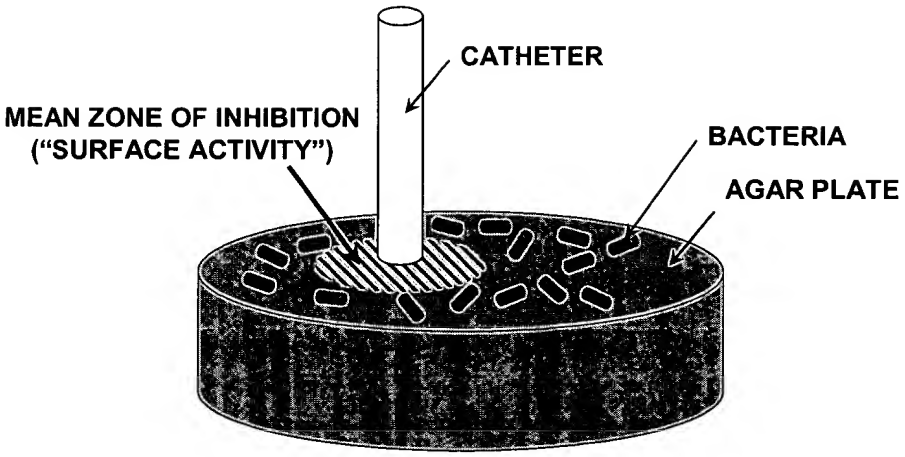

Figure: Design of Mermel Publication "Leaching" Experiments

On page 2, 7th paragraph, of the Office Action, the Examiner contended that in the Mermel Publication, "[t]he surface activity shows the instant conditions", apparently referring to the legend of Figure 1 in the Mermel Publication (page 923). This figure shows that the antimicrobial activity of the chlorhexidine-silver-sulfadiazine catheter is reasonably maintained (in contrast to the heparin or heparin/benzalkonium chloride catheters) for at least 48 hours of incubation in serum (see Mermel Publication, page 922, Figure 1). However, in contrast to the Examiner's argumentation, this not does not change the fact that throughout this time period, the mean zone of inhibition, i.e., the area through which biocidal amounts leached from the catheter, remained at about 10-11 mm (see y-axis of Figure 1). It would thus appear that the term "surface activity" quoted by the Examiner as "providing the instant conditions" (see above), in fact refers to the

mean zone of inhibition, i.e., surface area on the agar through which antimicrobial components leached from the catheter.

Such "leaching" characteristics were, in fact, presented as desirable by the Mermel Publication (page 923, 2nd column, 3rd full paragraph):

> It seems increasingly likely that engineering leachable antimicrobial activity onto the surface of a vascular catheter, whether by design or serendipitously in the case of heparin binding, holds much promise for significantly reducing the risk of catheter-related bloodstream infection.

Accordingly, since the chlorhexidine-silver-sulfadiazine catheter consistently and by design leached biocidal amounts of one or more antimicrobial components of its coating into the surrounding agar, and since the claims as amended herewith call for the antimicrobial metallic material being non-leachably bound to the matrix, the Mermel Publication cannot anticipate the claimed invention.

The Examiner has also rejected claims 25-28, 30-32, 35 and 36 as allegedly anticipated under 35 U.S.C. §102(b) by 5019096 by Fox et al (the "**Fox Patent**"). The substance of the Fox Patent, however, is clearly cumulative of the Mermel Publication, and provides no additional or alternative teachings relevant to the presently claimed invention. Briefly, the type of antimicrobial coating suggested by Fox comprises a matrix-forming polymer such as polyurethane, and a

combination of a silver salt and a biguanide (Fox Patent, col. 2, lines 9-30). This type of coating is described to have the following properties (Fox Patent, column 4, lines 31-37, emphasis added):

> ... the essential polymeric coating agent component of the coating vehicle is biomedical polyurethane, since it has been found unexpectedly that polymeric materials of this class enable the antimicrobial agent to be retained in an active state on the coated medical device and released over an appreciable period of time, e.g., from about 12 to in excess of 21 days, ...

As in the Mermel Publication, the Fox Patent catheters were tested by measuring the "zone of inhibition" for each catheter to confirm this leachability. The results, presented in Table V (column 17-18), as well as in the tables at column 20, lines 37-45; column 21, lines 59-67; column 26, line 62 to column 27, line 8; column 28, lines 23-30; and column 28, line 59 to column 29, line 15, show that all catheters had a zone of inhibition, i.e., "leaching distance", of at least 9 mm.

Finally, claim 1 of the Fox Patent recites, in part:

> ... wherein the matrix is effective to provide controlled release of the antimicrobial agent at a level sufficient to suppress infection when in contact with fluids ....

Thus, the controlled release, or leaching, of antimicrobial agent is an innate feature of the articles in both the Mermel Publication and the Fox Patent. Since the present claims all call, directly or indirectly, for an antimicrobial metallic

material non-leachably bound to the polymer matrix, neither one of these references anticipates the present claims.

The Examiner has also rejected claims 25-27, 31, 32, and 35 as allegedly anticipated under 35 U.S.C. §102(a) by JP 08176527 by Honda et al (the "**Honda Patent**").[1]

It is re-emphasized that the Honda Patent is not available as prior art to any of the instant claims. The table under "Remarks" shows that claim 25 and new claims 50-55 are fully supported by priority application PCT/US94/14636, filed December 19, 1994. Claim 27 is also supported by the PCT application, e.g., at page 15, 1st paragraph:

> In a preferred embodiment, the antimicrobial agent is a metal, metal oxide, metal salt, metal complex, metal alloy or mixture [sic] thereof ...

In addition, in contrast to the Examiner's contention that this priority application does not disclose cross-linking, the instant priority application teaches as follows, e.g., at page 7, 2nd full paragraph (emphasis added):

> Preferred agents include biguanide compounds or benzalkonium compounds. These agents may be attached to the substrate by covalent binding, ionic

[1] The undersigned, among the attorneys recently appointed to prosecute this application by the Applicant (see Revocation of Power of Attorney and Substitute Power of Attorney filed 6/23/2003), does not have access to the English version of the Honda patent filed by Applicant's previous counsel. It would be greatly appreciated if the Examiner could fax a copy of the English translation to the undersigned, at the fax number next to the signature below.

> interaction, coulombic interaction, hydrogen bonding, crosslinking (e.g., as crosslinked (cured) networks) or as interpenetrating networks, for example.

Thus, reconsideration and withdrawal of this rejection is respectfully solicited.

The Examiner has also rejected claims 25 and 27 as allegedly anticipated under 35 U.S.C §102(b) by JP 05033217 by Kawamura et al. (the "**Kawamura Patent**"),[2] contending that the Kawamura Patent discloses fiber polyurethane surfaces treated with polyhexamethylene biguanide and zinc oxide.

As best as it is understood, the Kawamura Patent does not anticipate claims 25 or 27, nor new claims 50-55, because the Kawamura Patent does not relate to a coated surface. The English Abstract of the Kawamura Patent reads as follows (emphasis added):

> A solution of polyurethane polymer is blended with porous silica microcapsules including an antimicrobial agent and amorphous silicate powder selected from a bivalent heavy metal of zinc, copper, or nickel, and the solution is spun.

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[2] The undersigned, among the attorneys recently appointed to prosecute this application by the Applicant (see Revocation of Power of Attorney and Substitute Power of Attorney filed 6/23/2003), does not have access to the English version of the Kawamura patent filed by Applicant's previous counsel. The undersigned has, however, received some understanding of the teachings of the Kawamura Patent by consulting with a Japanese translator. It would nevertheless be greatly appreciated if the Examiner could fax a copy of the English translation to the undersigned, at the fax number next to the signature below.

Accordingly, the Kawamura Patent's yarn is a homogenous blend of polyurethane polymer and other components, including antimicrobial components, and not yarn or any other article having an antimicrobial coating. It is further the understanding of the undersigned, there is no teaching that this yarn does not leach biocidal amounts of elutables, as the paragraph referred to by the Examiner apparently refers to that washing did not diminish the antimicrobial capability of the yarn, not that nothing actually leached from the yarn.

All claims, as amended herewith, calls for a coating immobilized on a surface of the article. Since Kawamura does not disclose a coated surface, much less immobilization of a coating on a surface or how to achieve such immobilization, the reference cannot anticipatory.

Also, on page 2 of Exhibit C enclosed with the December 5, 2002 response, it was shown that specific processes had to be applied to construct cationic polyurethane, for example, by using acetone. Upon information and belief, the Kawamura Patent does not disclose that the polyurethane is catonic, nor prepared by a process leading to a polycationic polyurethane.

The present claims are therefore novel over the Kawamura Patent, and reconsideration and withdrawal of this rejection is respectfully requested.

Double-Patenting

All claims have been rejected by the Examiner under the judicially created doctrine of obviousness-type double-patenting as being allegedly unpatentable over various claims in commonly-owned U.S. Patent 5,849,311.

It is submitted that a terminal disclaimer will be timely filed upon allowance of any conflicting claims in the instant application.

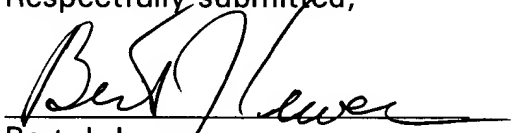
Concluding Remarks

It is noted that both the Fox Patent, the Honda Patent, and the Kawamura Patent have been cited in the prosecution of previous applications in the present patent application family (see, for example, U.S. Serial No. 08/742,580, issued as U.S. Patent No. 5,817,325) that is now issued as U.S. Patents. According to the understanding of the undersigned, after reviewing the prosecution history of these earlier cases, the non-leachability of the claimed compositions and methods has been among the features considered by the Examiner to distinguish the invention from the Fox Patent and the Kawamura Patent, as well as combinations thereof. Similarly, the Honda Patent has previously been overcome as prior art based on the earlier priority date of this patent application family. With the instant amendment, where the feature of non-leachability of the claimed coatings has been included into the claims, and where it has been shown that the claimed invention pre-dates the Honda Patent, it is believed that all rejections have

been overcome. Allowance of all claims as amended herewith is therefore earnestly solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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